Is Hyperinsulinemia Required to Develop Overeating-Induced Obesity?

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Type 2 diabetes is characterized by insulin resistance, and the hyperinsulinemia commonly observed in patients is thought to be a compensatory response. Yet it has been difficult to disentangle cause and effect. Mehran et al. (2012) provide genetic evidence that a reduction of insulin secretion prevents high-fat feeding-induced obesity.

Type 2 diabetes mellitus (DM2) is often associated with obesity, and both conditions are characterized by insulin resistance and increased insulin levels. Hyperinsulinemia is considered to be a compensatory response to insulin resistance, which allows us to maintain glucose and lipid homeostasis during states of increased insulin resistance such as illness or stress. In the clinic, it is almost always possible to control glycemia in individuals with DM2 by giving more insulin. However, there is also some data suggesting that prolonged hyperinsulinemia per se can induce insulin resistance. Thus the question of whether hyperinsulinemia is the "cart or the horse" is highly relevant—yet hard to dissect (reviewed in Shanik et al., 2008). Mehran et al. (2012) now reveal that lowering hyperinsulinemia has the beneficial effect of preventing high-fat feeding-induced obesity.

To study the role of hyperinsulinemia in obesity and insulin resistance, Mehran et al. (2012) used a genetic approach to limit insulin secretion from pancreatic β cells in mice. From a technical standpoint this was a complicated undertaking due to the fact that, whereas humans have only one insulin gene, mice have two, *Ins1* and *Ins2*. Further, insulin is expressed not only in pancreatic β cells but also in the brain, especially during development, where it conceivably could act locally and regulate neuronal development and energy homeostasis (Plum et al., 2006). Mehran et al. (2012) first demonstrated that only *Ins2* is expressed in the CNS, whereas *Ins1* is restricted to pancreatic β cells. They then generated a mouse model lacking both alleles of the *Ins2* gene and one allele of the *Ins1* gene. The resulting hypomorph *Ins1*+/−:*Ins2*−/− mice, which express insulin in β cells only, could then be compared to control mice. Although this approach reduced the expression of insulin mRNA in the pancreas by 50% as expected, insulin secretion was still comparable between *Ins1*+/−:*Ins2*−/− mice and controls, possibly due to posttranslational compensation.

To determine how Ins1 haploinsufficiency affects susceptibility to insulin resistance and obesity, the authors placed the mice on a high-fat diet. For the first few weeks, insulin secretion increased about 3-fold in the *Ins1*+/−:*Ins2*−/− mice, compared to about 6-fold in the controls. Surprisingly, however, whereas the controls gained significantly more weight on high-fat diet than animals on chow diet, the *Ins1*+/−:*Ins2*−/− mice did not. At 1 year of age, after 10 months of high-fat feeding, the *Ins1*+/−:*Ins2*−/− mice were still as lean as animals fed the control diet and protected from high-fat diet-induced hepatic steatosis and dyslipidemia, and they did not exhibit hyperinsulinemia anymore.

What do these findings tell us about the relative roles of insulin and adiposity in metabolic diseases? Most genetic mouse models protected from high-fat diet-induced obesity are also metabolically protected and, for example, do not develop hepatosteatosis and dyslipidemia. While the level of adiposity may appear to be the primary variable and, potentially, be seen as the driver of the metabolic phenotype, one should remember that the differences in adiposity are not only a consequence of increased adipocyte growth but are primarily due to alterations in energy expenditure. Indeed, while *Ins1*+/−:*Ins2*−/− mice have similar food intake as controls, they exhibit an increase in energy expenditure, which likely accounts for the differences in adiposity. Thus, the lack of dysmetabolic features could be a direct consequence of increased energy expenditure and decreased adiposity. Extensive gene-expression profiling of adipose tissue from *Ins1*+/−:*Ins2*−/− mice supports this notion. Mehran et al. (2012) observed increased expression of genes under the control of sympathetic outflow, such as uncoupling protein 1 (UCP1). Since UCP1 uncouples mitochondrial respiration from ATP production and facilitates the burning of energy, increased UCP1 expression may potentially account for some of the differences in energy expenditure. So how do *Ins1*+/−:*Ins2*−/− mice increase energy expenditure and thereby stay lean when fed a high-fat diet while control mice are unable to do so? It is likely that hyperinsulinemia creates a feed-forward loop via β cell insulin resistance that may increase basal insulin release in the context of overnutrition. But why is the initial hyperinsulinemia seen in the *Ins1*+/−:*Ins2*−/− mice not sufficient to do the same? One reason for the increased energy expenditure may be that lower hyperinsulinemia could allow for a higher sympathetic tone as insulin can reduce sympathetic outflow to adipose tissue. Although this is an important regulatory mechanism involved in the dynamic regulation of fasting to feeding transition (Scherer et al., 2011), chronic hyperinsulinemia may actually cause sympathetic insufficiency, which often is seen in obesity. The adipose tissue gene-expression profiles lend support to this hypothesis. Another possibility is that the *Ins1*+/−:*Ins2*−/− mice maintain a more

pulsatile insulin secretion profile and that this mechanism prevents the development of insulin resistance (Matveyenko et al., 2012) and possibly obesity, which may be the subject of future studies.

The authors were unable to show increased insulin resistance in high-fat-fed control mice, as this would be expected in this mouse strain, which could be due to a lack of sensitivity of the insulin tolerance test and would need to be tested with euglycemic clamp studies; it is therefore not definitive that Ins1 haploinsufficiency prevents high-fat diet-induced insulin resistance. It would be interesting to probe this question in the *Ins1*+/−:*Ins2*−/− mice or to replicate these findings in an inducible *Ins1*+/−:*Ins2*−/− model where haploinsufficiency for Ins1 can be induced in adulthood after normal development.

What are the clinical implications of these findings? Many interventions used to treat DM2, such as exercise, weight loss, and drugs, including metformin and tiazolidinediones, decrease circulating insulin levels. What remains unclear is how each drug affects insulin secretion independent of its effects on insulin action. It may be possible to specifically inhibit either insulin secretion or insulin signaling. For instance, K(ATP) channel openers, which reduce insulin secretion from β cells, such as diazoxide, would unlikely be safe in DM2 but may be beneficial in the prediabetic state before the onset of relative insulin deficiency. Alternatively, one could interfere with insulin binding to the insulin receptor through insulin antagonists (Schäffer et al., 2008). Reducing insulin signaling could mimic decreased pancreatic insulin secretion. However, such approaches would require significant further research to ensure their safety, as the risks of negatively affecting glycemic control are significant. A second important implication is that these studies point to the potential risk of over-treating type 2 diabetics with too much insulin and worsening insulin resistance. This concern is particularly relevant given that some insulin analogs, about to be introduced into clinical practice, have increasingly long half-lives that exceed 24 hr.

As any good research, Mehran et al. (2012) raises many questions that await answers. Thus, while the observation that Ins1 haploinsuficiency prevents high-fat feeding induced obesity is provocative, it would be important to determine if it prevents insulin resistance, as well.

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